Assignment 03

PUBH 8878

Requirements:

- Show complete mathematical work for any derivations.
- Submit well-documented R code with clear comments and set seeds.
- Interpret results in a genetic/biological context where applicable.
- Submit the rendered PDF; do not submit the source `.qmd`.
- You may reuse and adapt your Lab 03 code, but your write-up must be self-contained.

Problem 1: EM for ABO gene frequencies; derivation, inference, and sensitivity (25 pts)

Part A (15 pts)

Consider phenotype counts from the ABO system under Hardy–Weinberg equilibrium (HWE): n_A, n_{AB}, n_B, n_O with total N. Let genotype frequencies be $p_A^2, 2p_Ap_O, 2p_Ap_B, p_B^2, 2p_Bp_O, p_O^2$ and $p_O = 1 - p_A - p_B$.

Derive the EM updates shown in lecture. Specifically, show that the E-step allocations for A and B phenotypes are

$$\tilde{n}_{AA} = n_A \frac{p_A^2}{p_A^2 + 2p_Ap_O}$$

$$\tilde{n}_{AO} = n_A \frac{2p_Ap_O}{p_A^2 + 2p_Ap_O}$$

and similarly for BB, BO, and that the M-step is

$$p_A^{(t+1)} = \frac{2\tilde{n}_{AA} + \tilde{n}_{AO} + n_{AB}}{2N}$$

$$p_B^{(t+1)} = \frac{2\tilde{n}_{BB} + \tilde{n}_{BO} + n_{AB}}{2N}$$
$$p_O^{(t+1)} = 1 - p_A^{(t+1)} - p_B^{(t+1)}$$

Hint (how to derive EM generally):

1) Choose latent variables so the complete data are simple. Here, treat latent genotype counts,
$$(n_{AA}, n_{AO}, n_{AB}, n_{BB}, n_{BO}, n_{OO})$$
as missing, with only phenotype totals observed.

2) Write the complete-data log-likelihood

$$\begin{aligned}\ell_c(p_A, p_B) =& n_{AA}\log p_A^2 + n_{AO}\log(2p_A p_O) + n_{AB}\log(2p_A p_B) + \\ & n_{BB}\log p_B^2 + n_{BO}\log(2p_B p_O) + n_{OO}\log p_O^2\end{aligned}$$

using $p_O = 1 - p_A - p_B$.

3. E-step: replace latent counts by their conditional expectations given the observed phenotypes under current parameters, e.g., for phenotype A, and form $Q(p \,|\, p^{(t)}) = \mathbb{E}[\ell_c(p) \mid \text{data}, p^{(t)}]$.
4. M-step: M-step: Maximize $Q(p|p^{(t)})$ subject to $p_A + p_B + p_O = 1$. Hint: Consider rewriting the objective in terms of allele counts rather than genotype counts.

Part B (10 pts)

Consider two biallelic SNPs with haplotypes $\{ab, aB, Ab, AB\}$ under HWE and unphased genotypes $(g_1, g_2) \in \{0, 1, 2\}^2$. Note that (ab, ab) yields $(0, 0)$, (ab, aB) or (ab, Ab) yields $(0, 1)$, (AB, AB) yields $(2, 2)$, etc.

Show that if every observed genotype is $(1, 1)$, then $P\{(1, 1)\} = 2\left(p_{ab}p_{AB} + p_{aB}p_{Ab}\right)$ and the likelihood depends only on the cross-sum $S = p_{ab}p_{AB} + p_{aB}p_{Ab}$ (a ridge; parameters not identifiable).

Problem 2: Two-point linkage — LOD and support intervals (25 pts)

Suppose one heterozygous transmitting parent (A/a and B/b) is crossed to an $aabb$ mate, yielding child haplotype counts $(n_{AB}, n_{Ab}, n_{aB}, n_{ab})$. Let $n_{\text{NR}} = n_{AB} + n_{ab}$ and $n_{\text{R}} = n_{Ab} + n_{aB}$.

Part A: LOD from counts (10 pts).

Show that for a given recombination fraction $\theta \in (0, 0.5)$ the two-point LOD relative to independence ($\theta = 0.5$) is

$$\mathrm{LOD}(\theta) = \log_{10}\left\{ \frac{\theta^{\,n_{\mathrm{R}}}(1-\theta)^{\,n_{\mathrm{NR}}}}{0.5^{\,n_{\mathrm{R}}+n_{\mathrm{NR}}}} \right\}.$$

Derive the MLE $\hat{\theta}$ and show it equals $n_{\mathrm{R}}/(n_{\mathrm{R}} + n_{\mathrm{NR}})$ when $0 < \hat{\theta} < 0.5$.

Part B: Unknown phase and LD-informed LOD (15 pts)

A heterozygous transmitting parent $(A/a,\ B/b)$ has **unknown phase**: either **coupling** (AB/ab) or **repulsion** (Ab/aB). Let

$$n_{\mathrm{NR}} = n_{AB} + n_{ab}, \qquad n_{\mathrm{R}} = n_{Ab} + n_{aB}, \qquad N = n_{\mathrm{NR}} + n_{\mathrm{R}}.$$

Let $w = \Pr\{\text{coupling } (AB/ab)\}$ and $1 - w = \Pr\{\text{repulsion } (Ab/aB)\}$.

(i) Mixture likelihood (5 pts).
Show that with unknown phase the observed-data likelihood is a **mixture** of the two phase-specific binomial likelihoods:

$$L(\theta; w) = w\,(1-\theta)^{\,n_{\mathrm{NR}}}\,\theta^{\,n_{\mathrm{R}}} \;+\; (1-w)\,(1-\theta)^{\,n_{\mathrm{R}}}\,\theta^{\,n_{\mathrm{NR}}}.$$

Hence the two-point LOD relative to independence ($\theta = 0.5$) is

$$\mathrm{LOD}(\theta; w) = \log_{10}\left\{ \frac{w\,(1-\theta)^{\,n_{\mathrm{NR}}}\theta^{\,n_{\mathrm{R}}} + (1-w)\,(1-\theta)^{\,n_{\mathrm{R}}}\theta^{\,n_{\mathrm{NR}}}}{0.5^{\,N}} \right\}.$$

(ii) Linking LD to w (5 pts).
Let population haplotype frequencies be $p = (p_{ab}, p_{aB}, p_{Ab}, p_{AB})$ (sum to 1).
Condition on the parent being the **double heterozygote** $(g_1, g_2) = (1, 1)$. Use Bayes' rule to show

$$w = \Pr\{(ab, AB) \mid (1,1)\} = \frac{p_{ab}\,p_{AB}}{p_{ab}\,p_{AB} + p_{aB}\,p_{Ab}},$$

$$1 - w = \frac{p_{aB}\,p_{Ab}}{p_{ab}\,p_{AB} + p_{aB}\,p_{Ab}}.$$

Define $D = p_{ab}p_{AB} - p_{aB}p_{Ab}$ and note that $\mathrm{sign}(D)$ indicates whether **coupling** $(D > 0)$ or **repulsion** $(D < 0)$ phase is a priori more likely.

(iii) Quick numerical check (5 pts).
Take $p^\star = (0.40, 0.10, 0.25, 0.25)$.
Compute w and $1-w$. Then, using the example counts $(n_{AB}, n_{Ab}, n_{aB}, n_{ab}) = (18, 5, 4, 17)$ (so $N = 44$, $n_{\mathrm{R}} = 9$, $n_{\mathrm{NR}} = 35$), evaluate and **compare** $\mathrm{LOD}(\hat{\theta}; w = \frac{1}{2})$ versus $\mathrm{LOD}(\hat{\theta}; w)$ at $\hat{\theta} = n_{\mathrm{R}}/N$.
Briefly explain (one sentence) how LD information ($w \neq \frac{1}{2}$) can increase or decrease the peak LOD when phase is unknown.

Problem 3: Two-SNP haplotype EM and LD measures (25 pts)

Part A (10 pts)

For two biallelic SNPs with haplotypes $\{ab, aB, Ab, AB\}$ at frequencies $\{p_{ab}, p_{aB}, p_{Ab}, p_{AB}\}$ (summing to 1), enumerate the possible haplotype pairs consistent with each unphased genotype $(g_1, g_2) \in \{0, 1, 2\}^2$.

Show that only $(g_1, g_2) = (1, 1)$ is ambiguous with two possible pairs: (ab, AB) and (aB, Ab).

Part B (10 pts)

Simulate $N = 1000$ individuals from true haplotype frequencies $p^\star = (0.40, 0.10, 0.25, 0.25)$ and estimate $\hat{p}$ via EM from a uniform start. Report $\hat{p}$ and absolute errors $|\hat{p} - p^\star|$.

Note that the E-step weights for $(1, 1)$ are proportional to $p_{ab}p_{AB}$ and $p_{aB}p_{Ab}$, and the M-step update is $p^{(t+1)} = (\text{expected hap counts})/(2N)$.

Here is a sample R code snippet to get you started:

```r
set.seed(8878)

N <- 1000
p_true <- c(ab = 0.40, aB = 0.10, Ab = 0.25, AB = 0.25)

# helper: draw N unordered haplotype pairs, then make unphased genotypes (g1,g2)
draw_genotypes <- function(N, p) {
    # code haplotypes to allele counts (B allele) at SNP1, SNP2
    H <- rbind(ab = c(0, 0), aB = c(0, 1), Ab = c(1, 0), AB = c(1, 1))
    hap1 <- sample(rownames(H), size = N, replace = TRUE, prob = p)
    hap2 <- sample(rownames(H), size = N, replace = TRUE, prob = p)
    G <- H[hap1, ] + H[hap2, ] # N x 2 matrix with entries in {0,1,2}
    as.data.frame(G) |>
        setNames(c("g1", "g2"))
```

```
}

# simulate data
dat <- draw_genotypes(N, p_true)
```

Part C (5 pts)

Compute $D = p_{11} - p_{B1}p_{B2}$ with $p_{11} = p_{AB}$, $p_{B1} = p_{Ab} + p_{AB}$, $p_{B2} = p_{aB} + p_{AB}$. Report D and $r^2 = D^2/(p_{B1}(1-p_{B1})p_{B2}(1-p_{B2}))$. Comment on how LD would affect single-marker association at either SNP.

Problem 4: Single-marker association with QC and LD attenuation (25 pts)

Simulate $n = 2000$ unrelated individuals. Let a causal biallelic SNP C have MAF 0.30 and generate a quantitative trait Y with additive effect size $\beta_C = 0.50$ (per allele) and noise $\epsilon \sim \mathcal{N}(0, 1)$. Let a tag SNP T be in LD with C such that $r = \text{corr}(G_C, G_T) = 0.8$ and both are in HWE. Let T have MAF 0.30.

Part A (15 pts)

Generate (G_C, G_T, Y) by first simulating haplotypes for (C, T) with a chosen LD structure that yields $r \approx 0.8$, then form genotypes and $Y = \beta_C G_C + \epsilon$. Fit simple linear models $Y \sim G_C$ and $Y \sim G_T$ and report $\widehat{\beta}_C$ and $\widehat{\beta}_T$, alongside their 95% confidence intervals.

Part B (10 pts)

Introduce a basic QC step: test HWE in the controls of a case–control subsample formed by thresholding Y at its 80th percentile to define cases (cases are the top 20% of Y). Compute an exact or χ^2 HWE p-value in controls for T; state whether you would flag T using a threshold of 10^{-6} and why QC is typically done in controls only.